Chemistry 17: Section Handout 9

Topics: *addition of electrophiles to alkenes: hydrohalogenation, hydration, bromination, halohydrin and haloether formation, epoxidation, formal hydration by oxymercuration or hydroboration*

Key Concept Review

Vocabulary for Describing Reaction Mechanisms

Stereospecific: Describes a mechanism in which the stereochemistry of the products is dictated by the stereochemistry of the starting material. A "non-stereospecific" mechanism is one in which stereochemical information is lost. A stereospecific mechanism in which the products have the same configuration as the starting material proceeds with *stereoretention*. A stereospecific mechanism in which the products have the opposite configuration as the starting material proceeds with *stereoinversion.*

Stereoselective: Describes a mechanism in which there is a preference for formation of one stereoisomer over another, when both products can be formed by the same mechanism.

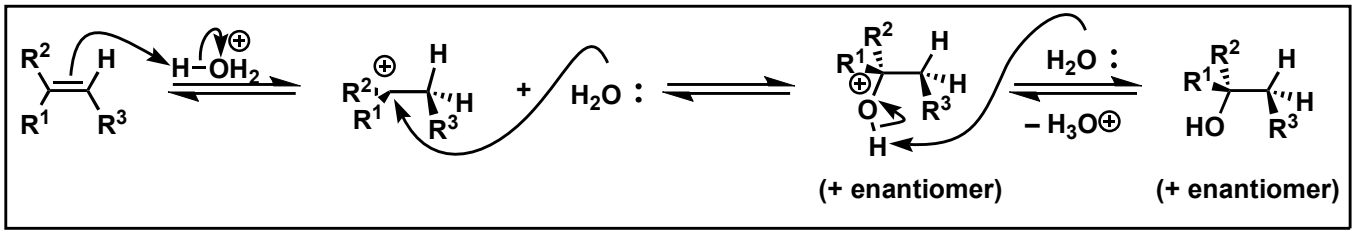
Regioselective: Describes a mechanism in which there is a preference for formation of one structural isomer over another, where both products can be formed through the same mechanism from the same starting material.

Markovnikov: Describes the more substituted regioisomer of product formed in the reaction class of electrophilic additions to alkenes proceeding through a full or partial carbocationic intermediate. Because the carbocation exists at the more stable (generally more substituted) position, trapping that carbocation with a nucleophile gives the more substituted regioisomer of product.

Anti-Markovnikov: Describes the less substituted regioisomer of product formed in the reaction class of concerted electrophilic additions to alkenes.

Alkene Additions Involving Carbocation Intermediates

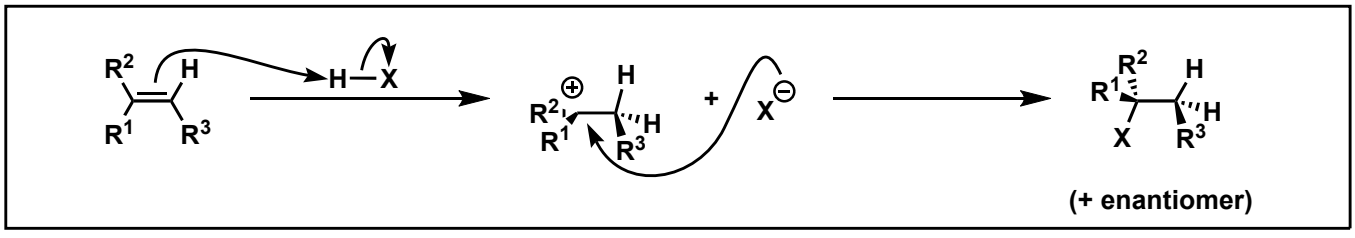
Acid-Catalyzed Hydration: The stepwise acid-catalyzed hydration mechanism involves protonation of the alkene with a strong acid to generate a carbocationic intermediate, followed by attack with water on the carbocation.



• *Regioselectivity:* Protonation occurs to form the more stable carbocationic intermediate. Subsequent nucleophilic attack on the carbocation gives Markovnikov substitution.

• *Stereospecificity:* The mechanism is NOT stereospecific. The nucleophile can add to either face of the carbocationic intermediate, but may be stereoselective if diastereomeric products are possible.

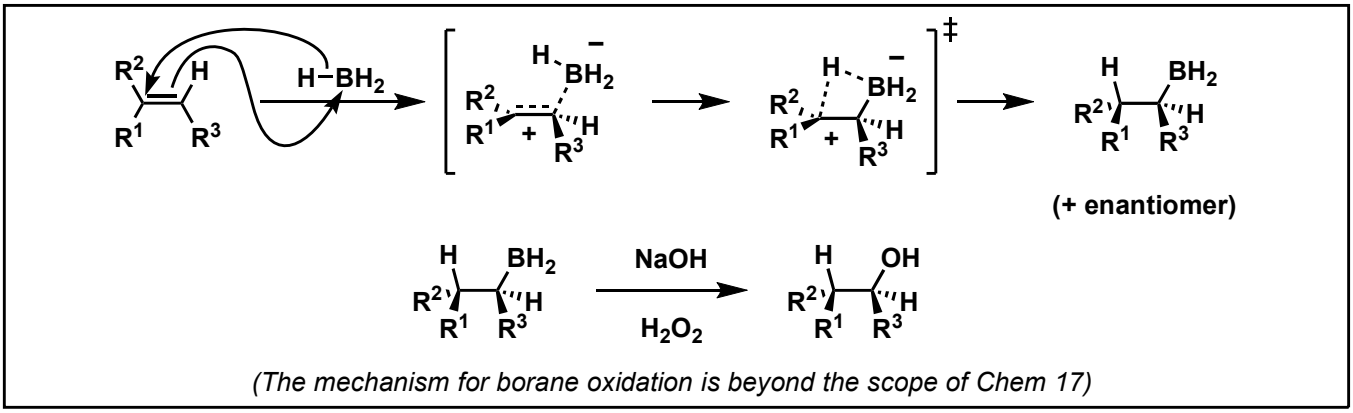
Hydrohalogenation: The stepwise hydrohalogenation mechanism involves protonation of the alkene with a strong acid to generate a carbocationic intermediate, followed by attack of a halide ion on the carbocation.



• *Regioselectivity:* Protonation occurs to form the more stable carbocationic intermediate. Subsequent nucleophilic attack on the carbocation gives Markovnikov substitution.

• *Stereospecificity:* The mechanism is NOT stereospecific. The nucleophile can add to either face of the carbocationic intermediate, but may be stereoselective if diastereomeric products are possible.

Hydroboration/Oxidation: The hydroboration mechanism involves the concerted, but highly asynchronous, addition of H–BH_2 across the alkene. Because the hydroboration mechanism is asynchronous, it may be helpful to think of it as a stepwise reaction in which the alkene attacks the empty p-orbital of BH_3 to generate a zwitterionic intermediate that quickly collapses. The oxidation step occurs as a separate reaction in which boron is replaced with a hydroxyl group to generate a "formal hydration" product.

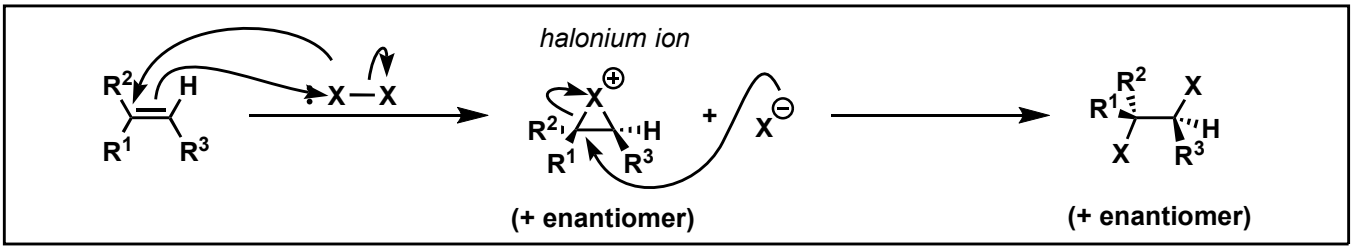


(The mechanism for borane oxidation is beyond the scope of Chem 17)

• *Regioselectivity: B*oron adds to the less substituted carbon (anti-Markovnikov) to place the partial positive charge in the transition state on the more substituted carbon.
• *Stereospecificity: H a*nd BH_2 add to the same face of the alkene to generate the syn product, and the subsequent oxidation step is stereospecific (stereoretentive). As such, the syn arrangement of H with OH is preserved in the formal hydration product.

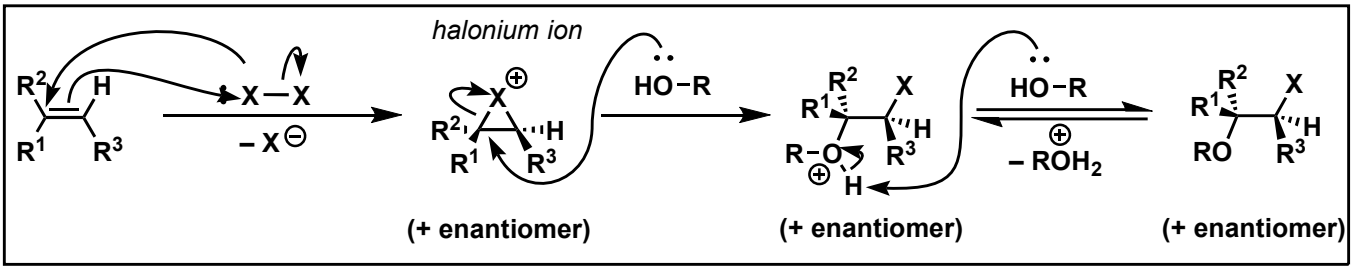
Alkene Additions Involving 3-Membered Ring Intermediates

Dihalogenation: The dihalogenation mechanism involves concerted addition of X_2 to form a halonium ion intermediate, followed by stereospecific and regioselective ring-opening with a halide ion, X^{-}.



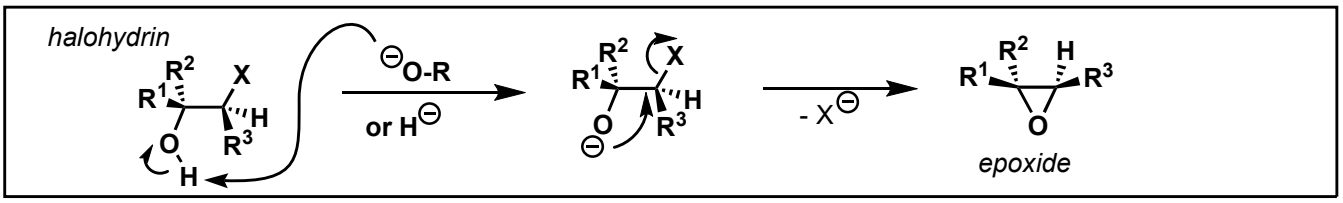
• *Regioselectivity:* Nucleophilic attack on halonium occurs at the more substituted carbon (Markovnikov) because it carries more carbocation character.
• *Stereospecificity:* Halonium ion formation is stereospecific, and nucleophilic attack occurs from the opposite face of the halonium to generate the anti product.

Haloetherification/Halohydration: The haloetherification mechanism involves concerted addition of X_2 to form a halonium ion intermediate, just as in the dihalogenation mechanism. The second step then involves stereospecific and regioselective ring-opening with an alcohol or water instead of a halide ion.

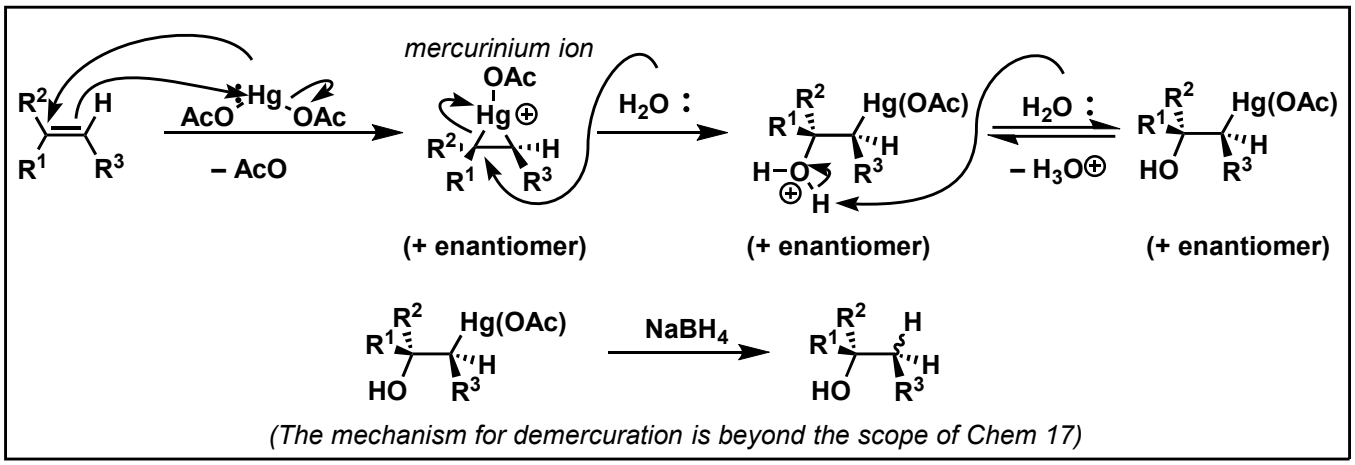


• *Regioselectivity:* Nucleophilic attack on halonium occurs at the more substituted carbon (Markovnikov) because it carries more carbocation character.
• *Stereospecificity:* Halonium ion formation is stereospecific, and nucleophilic attack occurs from the opposite face of the halonium to generate the anti product.

• Halohydrins can be converted stereospecifically to epoxides by deprotonation then intramolecular S_N2.

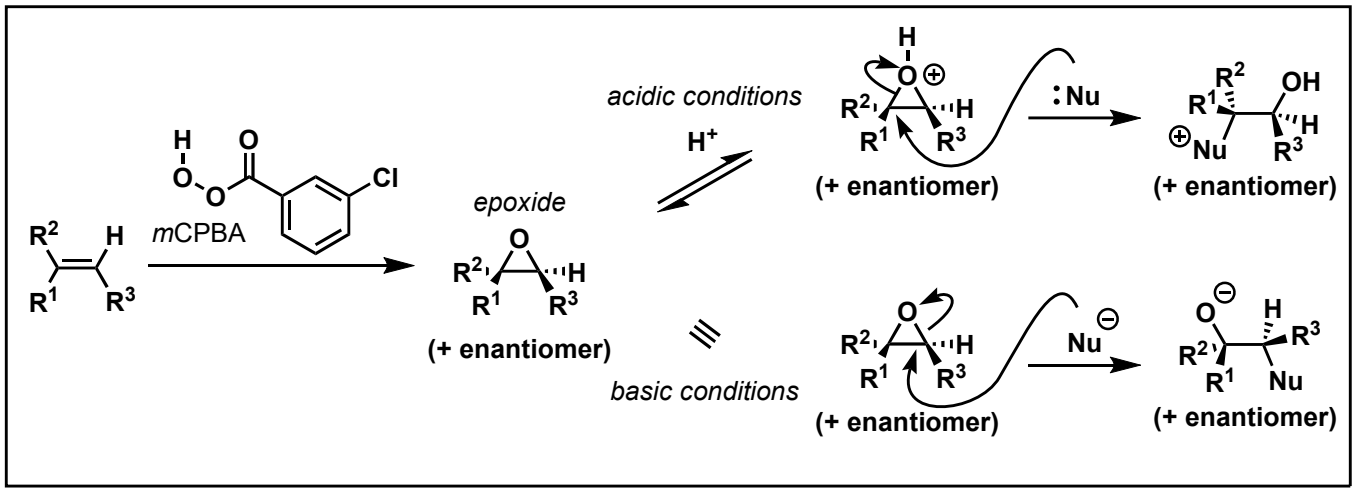


Oxymercuration/Demercuration: The oxymercuration mechanism involves concerted addition of $Hg(OAc)_2$ to generate a mercurinium ion intermediate**.** The second step then involves stereospecific and regioselective ring-opening with water. In another reaction, mercury is removed to generate a "formal hydration" product.



• *Regioselectivity:* Nucleophilic attack on mercurinium ion occurs at the more-substituted carbon (Markovnikov) because it carries more carbocation character.
• *Stereospecificity:* Nucleophilic attack occurs from the opposite face of the mercurinium to generate the anti product, BUT the subsequent demercuration step is NOT stereospecific. As such, the stereochemical information is lost in the formal hydration product.

Epoxide ring-opening: The epoxidation mechanism involves concerted addition of an electrophilic oxygen source (like *m*CPBA) to generate a stable, neutral epoxide**.** The epoxide may then be opened in another reaction under acidic or basic conditions.



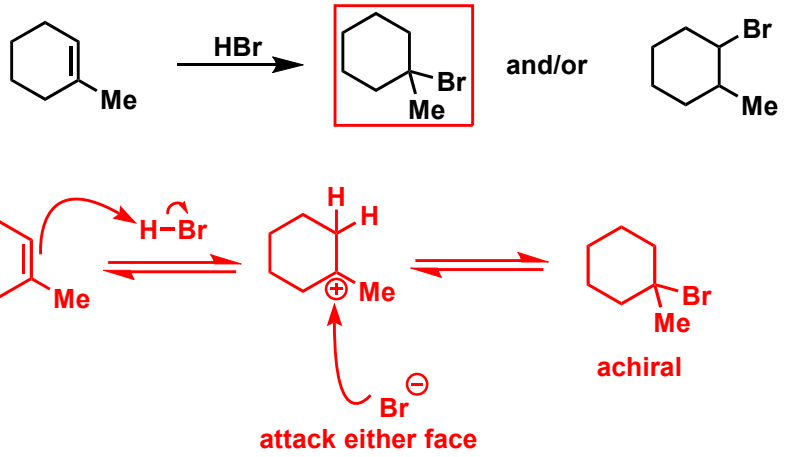
• *Regioselectivity under acidic conditions:* Nucleophilic attack on the epoxide occurs at the more substituted carbon under acidic conditions because it carries more carbocation character.
• *Regioselectivity under basic conditions:* Nucleophilic attack on the epoxide occurs at the less substituted carbon under basic conditions to avoid steric clash.
• *Stereospecificity:* Ring opening is stereospecific as nucleophilic attack occurs from the opposite face of the epoxide to generate the anti product. This leads to inversion on the attacked carbon, and retention of stereochemistry on the other carbon.

Workshop Problems

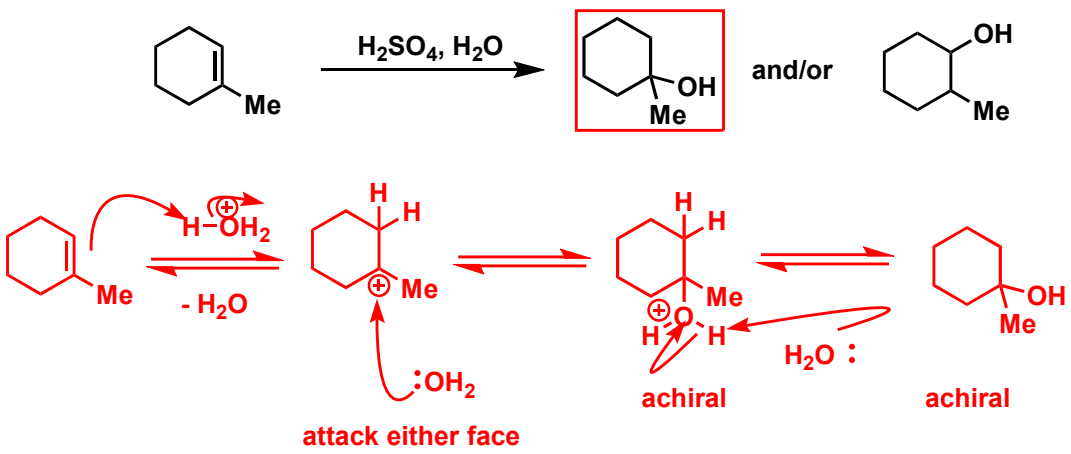
Workshop Problem 1: Additions to Alkenes

For each reaction involving the addition of electrophiles to isolated alkenes, shown below, propose a mechanism to account for the formation of the provided product(s), using curved arrows to represent the redistribution of electron density in each step. If regioisomeric products are provided, indicate which regioisomer(s) form. Redraw the product(s) with the appropriate stereochemistry. If multiple products are formed, indicate whether they are structural isomers, enantiomers, or diastereomers.

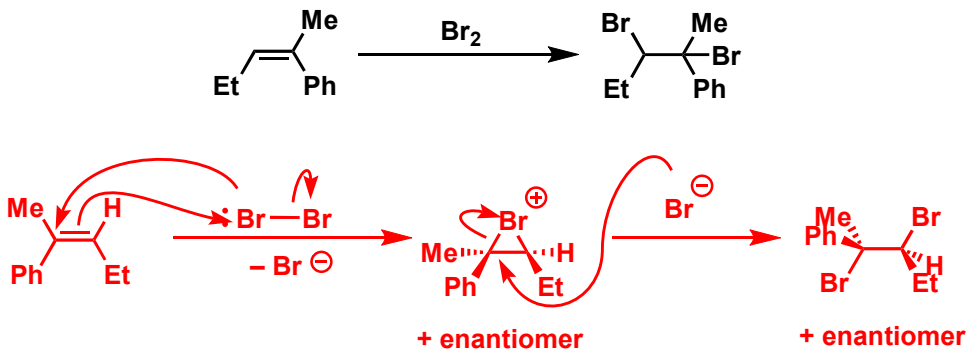
1-a.



1-b.



1-c.



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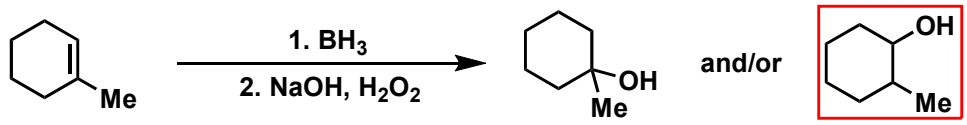
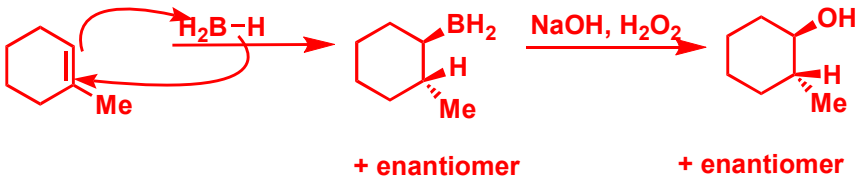
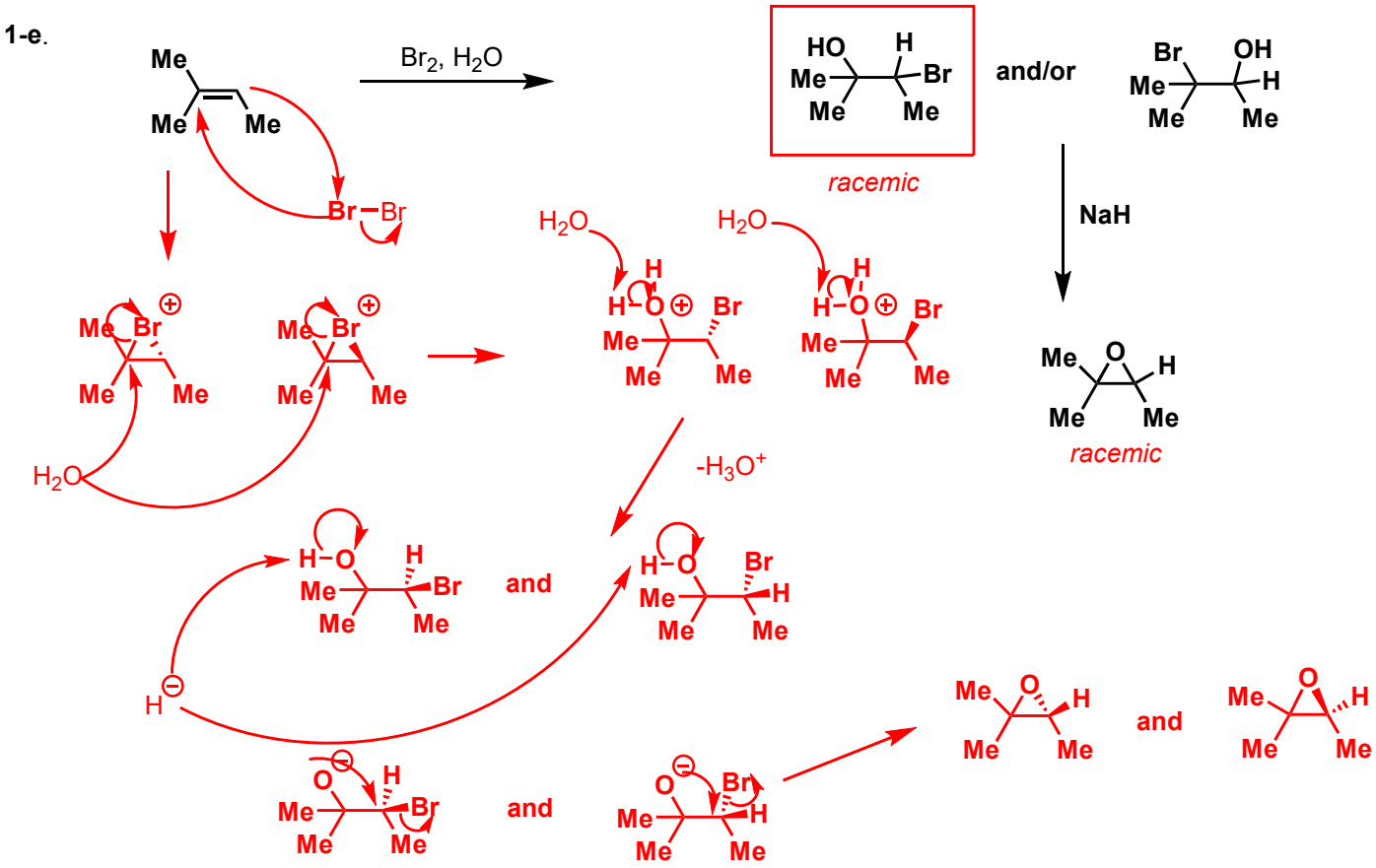
1-d.



Note: You do not need to show a mechanism for step 2.



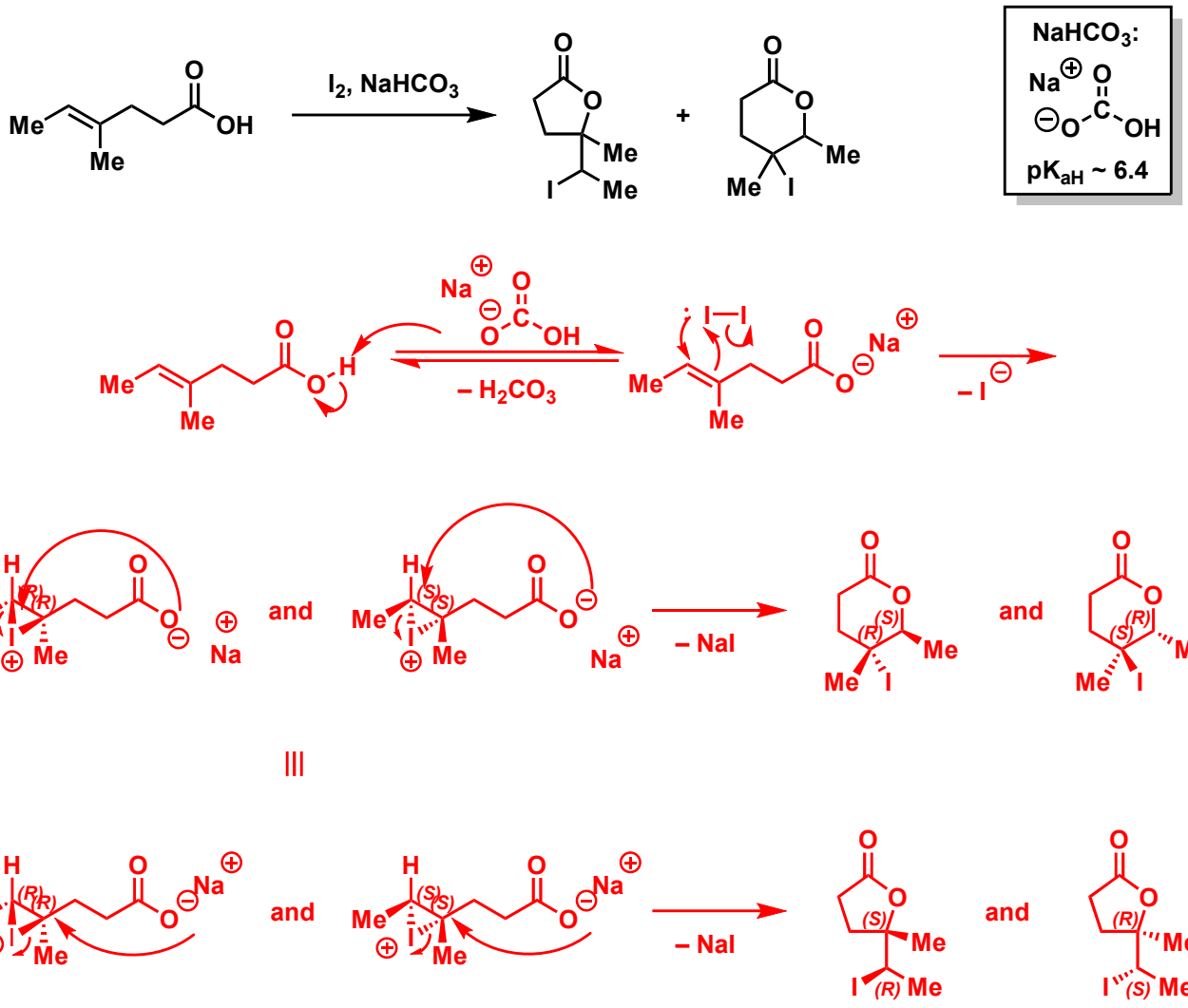
1-e.



Workshop Problem 2: Halocyclization Reactions

Halocyclization reactions (including iodolactonization) are useful for constructing highly functionalized rings; these reactions involve the net addition of a halogen and a heteroatom across an alkene.

2-a. Propose a mechanism for iodolactonization below in which 2 different products are observed. Use curved arrows to represent the redistribution of electron density in each step, and redraw the product(s) with the appropriate stereochemistry. (A lactone is a cyclic ester).



2-b. Please indicate which product in part **b** is the ***kinetic*** product and which is the ***thermodynamic*** product. Explain your reasoning in 1-2 sentences.

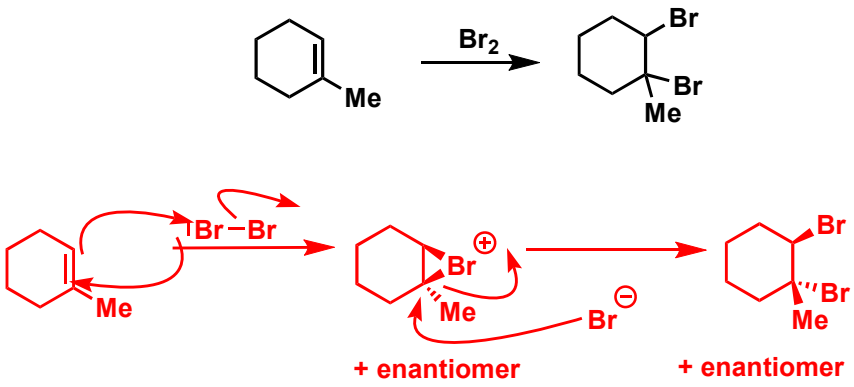
The 5-membered ring product will be the kinetic product. The more substituted carbon of the iodonium ion will stabilize the buildup of partial positive charge, causing that site to be more electrophilic and favoring the 5-membered ring formation.

The 6-membered ring product will be the thermodynamic product, because the 6-membered ring will be less strained than the 5-membered ring.

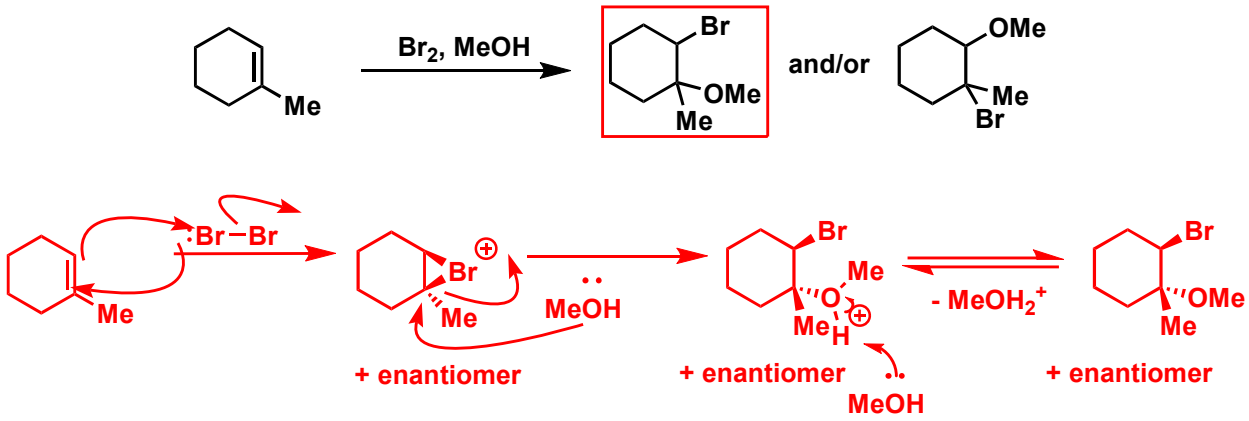
Skillbuilder Problem 1: Additions to Alkenes

For each reaction involving the addition of electrophiles to isolated alkenes, shown below, propose a mechanism to account for the formation of the provided product(s), using curly arrows to represent the redistribution of electron density in each step. If regioisomeric products are provided, indicate which regioisomer(s) form. Redraw the product(s) with the appropriate stereochemistry. If multiple products are formed, indicate whether they are structural isomers, enantiomers, or diastereomers.

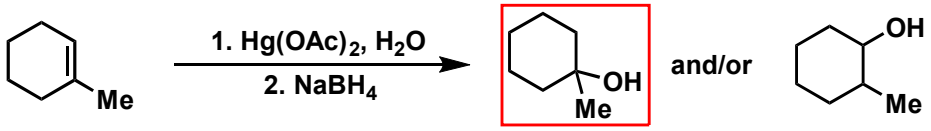
1-a.



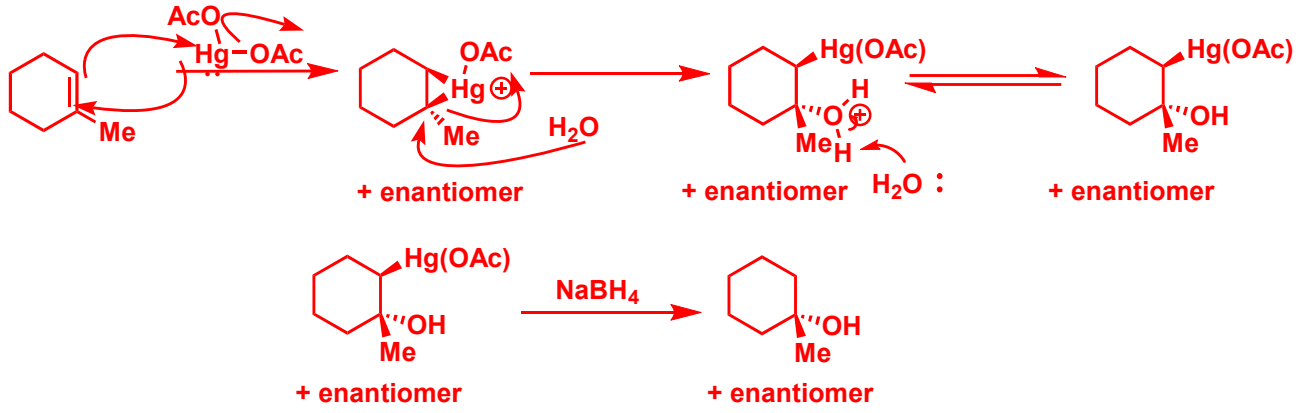
1-b.



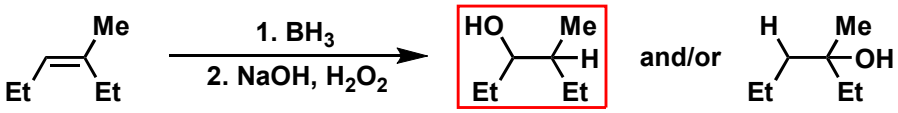
1-c.



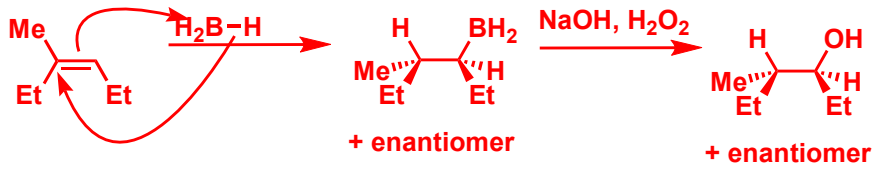
Note: You do not need to show a mechanism for step 2.



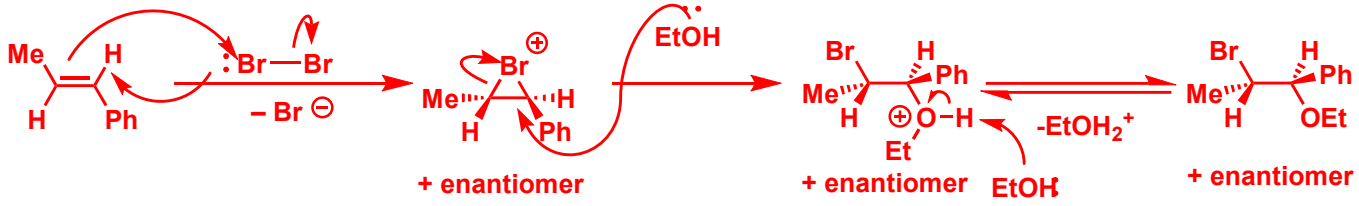
1-d.



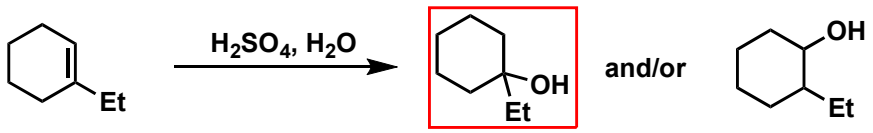
Note: You do not need to show a mechanism for step 2.

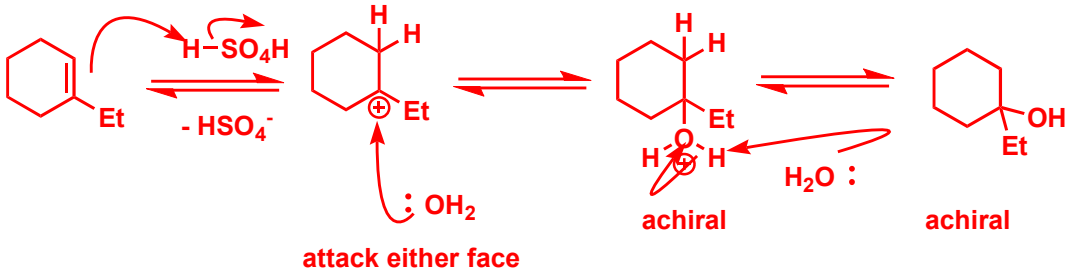


1-e.



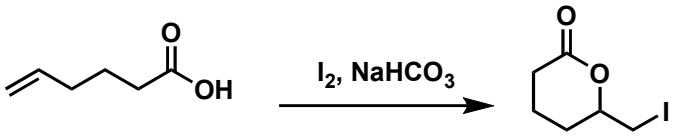
1-f.

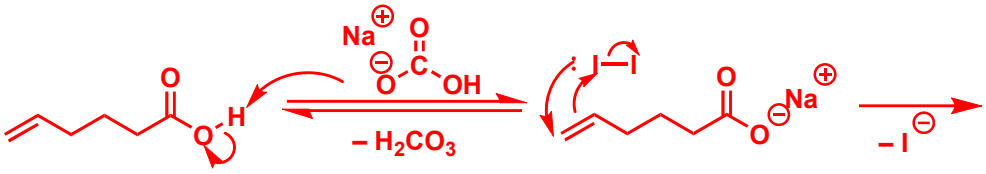


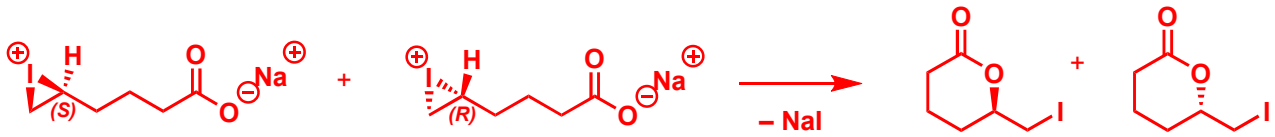


Skillbuilder problem 2: Iodolactonization

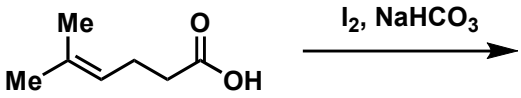
2-a. Propose a mechanism for iodolactonization below. Use curved arrows to represent the redistribution of electron density in each step, and redraw the product(s) with the appropriate stereochemistry. (A lactone is a cyclic ester). ***This problem is related to workshop problem 2.***







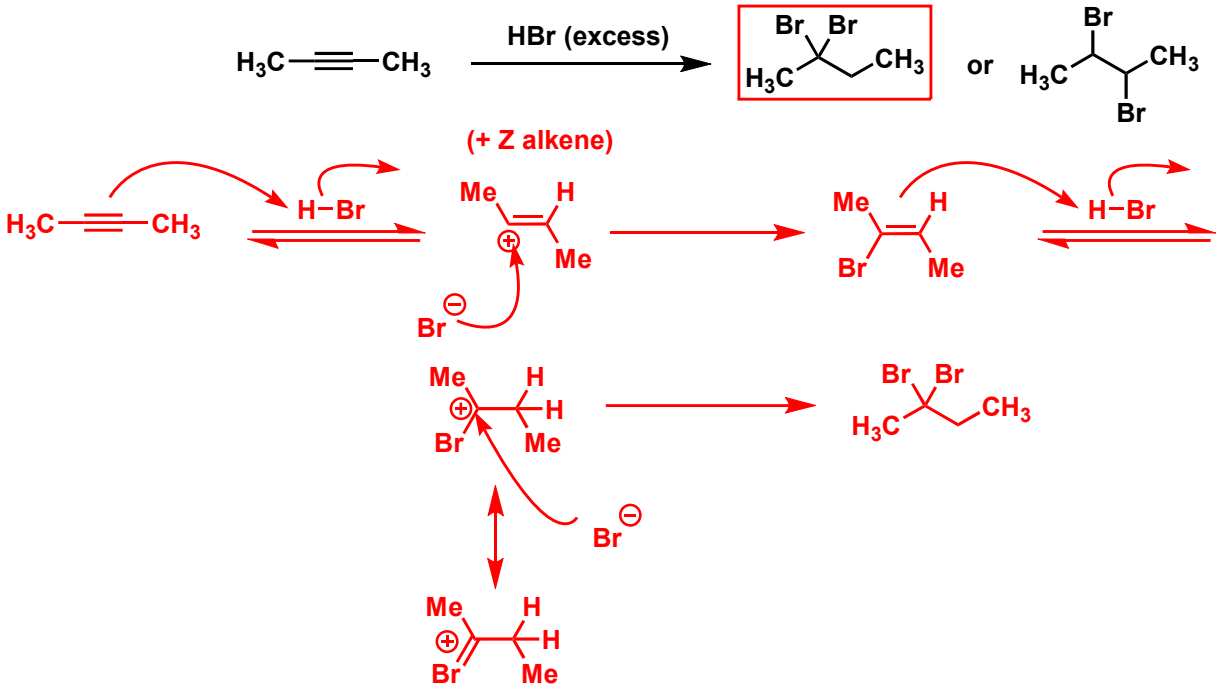
2-b. If the substrate is modified further from that given in Workshop problem 2-a. predict the major product of this iodolactonization and explain your reasoning in one sentence. You do not need to provide a complete mechanism, but drawing the key iodonium intermediate will likely aid your analysis.



Now the 6-membered ring product is both the thermodynamic and kinetic product as it has minimal strain and it forms when the carboxylate attacks the more-substituted, more-electrophilic side of the iodonium intermediate.

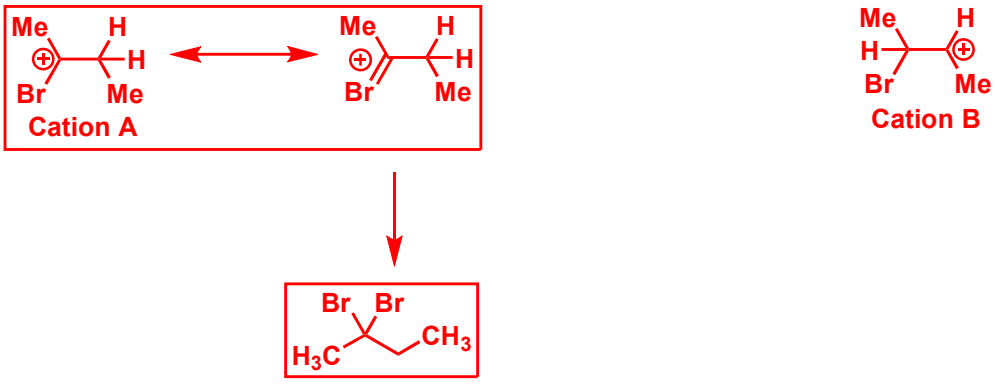
Challenge Problem =1: Predicting Regioselectivity in Unfamilar Reactions

1-a. HBr adds *twice* to alkynes, each time using the same mechanism as for addition to alkenes. Propose a mechanism to account for the formation of the product, using curved arrows to represent the redistribution of electron density in each step, and use your mechanism to predict which regioisomer forms.



1-b. Justify why the product(s) in part **a** form with the regioselectivity you indicated in your mechanism.

Bromine is not exceptionally electronegative (it is slightly less electronegative than nitrogen), so it has a minimal inductively-withdrawing effect on the carbocation A. It does, however, have high-lying lone pairs that can weakly (due to poor spatial overlap) donate to the vacant p-orbital of cation A, stabilizing it. Cation B cannot be stabilized in this way, so carbocation A is formed, dictating regioselective formation of the gem-dibrominated product.

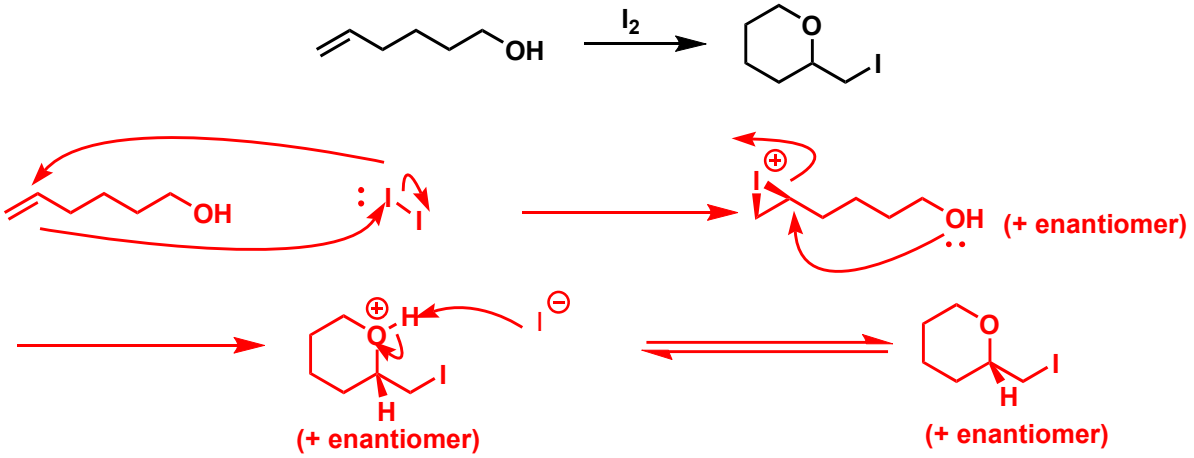


gem-dibrominated product

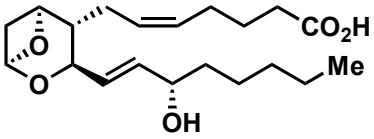
Challenge Problem 2:

Halocyclization reactions (including intramolecular iodoetherifications) are useful for constructing highly functionalized rings; these reactions involve the net addition of a halogen and a heteroatom across an alkene.

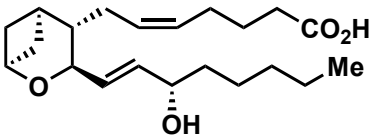
2-a. Propose a mechanism for iodoetherification below, using curly arrows to represent the redistribution of electron density in each step, and redraw the product(s) with the appropriate stereochemistry.



2-b. Thromoxane A_2 is a highly unstable yet biologically important molecule that stimulates platelet aggregation and contributes to blood clotting. The synthesis of a stable cyclobutane analog for biological studies was pursued by E.J. Corey here at Harvard nearly thirty years ago.

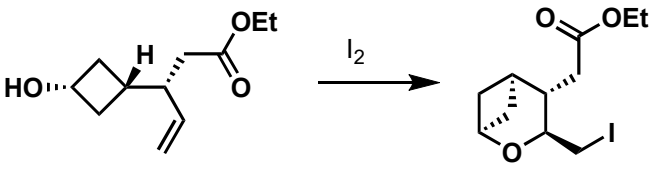


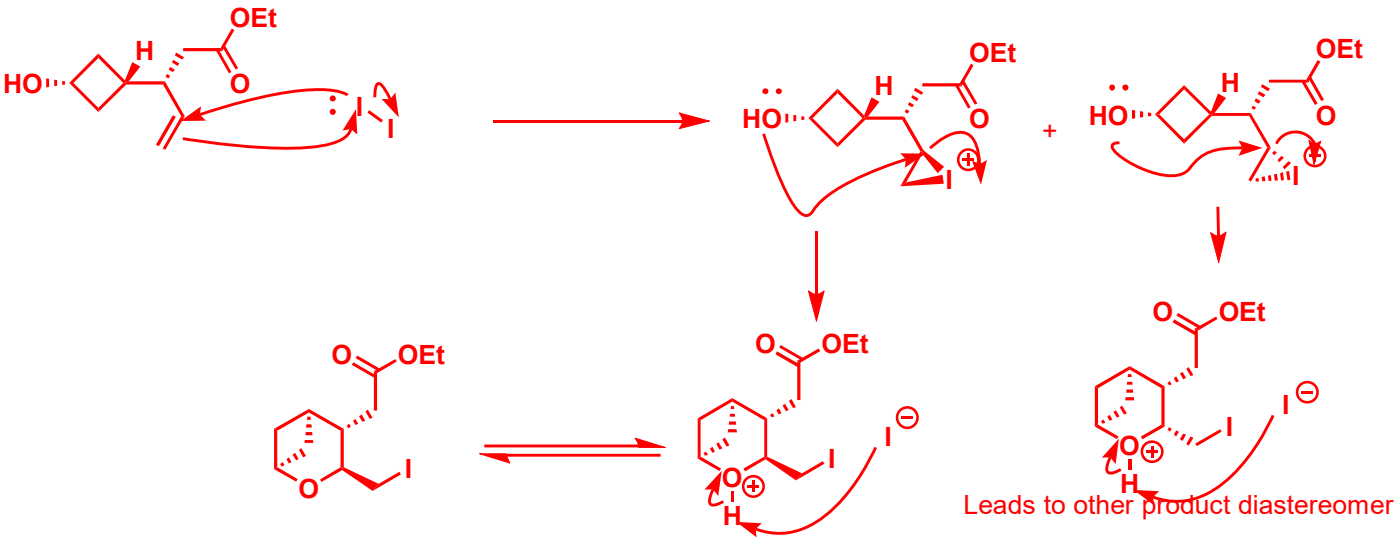
Thromboxane A_2



Cyclobutane analog

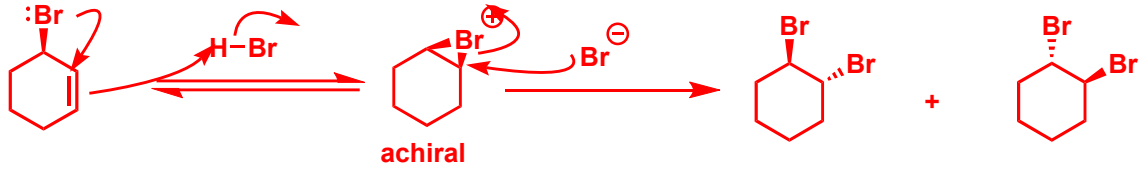
The iodoetherification below was attempted during the synthesis of the cyclobutane analog. Propose a mechanism for the transformation, using curly arrows to represent the redistribution of electron density in each step, and carefully shown the appropriate stereochemistry in each of the intermediates.





Challenge Problem 3: Stereospecificity

HBr addition is typically not stereospecific. However, in the case illustrated below, only the *anti* product is observed. Propose a mechanism for the transformation, using curly arrows to represent the redistribution of electron density in each step, and use your mechanism to justify the unusual stereospecificity.



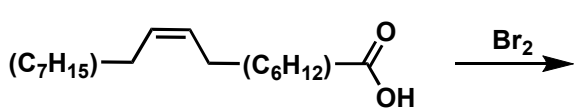
attack on other side gives the enantiomer of product

Usually hydrobromination proceeds through a planar carbocationic intermediate and in a non-stereospecific second step, bromide can add to either face of that cation to give syn and anti addition products. In this case, however, as the carbocation is generated by protonation, it can be trapped intramolecularly by the lone pairs on the adjacent bromine atom, forming a bromonium ino intermediate. Opening of a bromonium ion does proceed stereospecifically and the bromide nucleophile approaches the back face of the bromonium ion, giving exclusively the "anti" product.

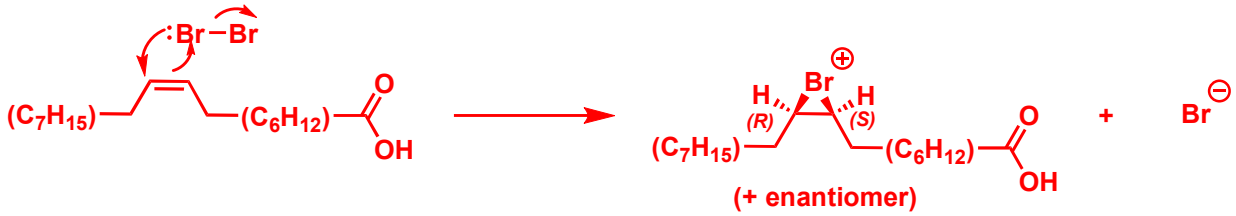
Challenge Problem 4: Stereospecificity

The bromine test for unsaturation can be used to determine the relative abundance of unsaturated fats in a lipid sample. The test is performed by adding a solution of bromine dropwise until a red color persists (Br_2 is red in color).

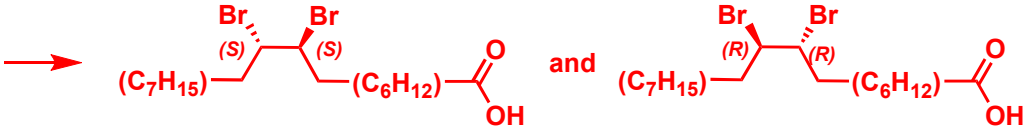
4-a. Propose a mechanism to account for the reaction of *cis*-oleic acid in the bromine test, using curved arrows to represent the redistribution of electron density in each step. Redraw the resulting product(s) with the appropriate relative and absolute stereochemistry.



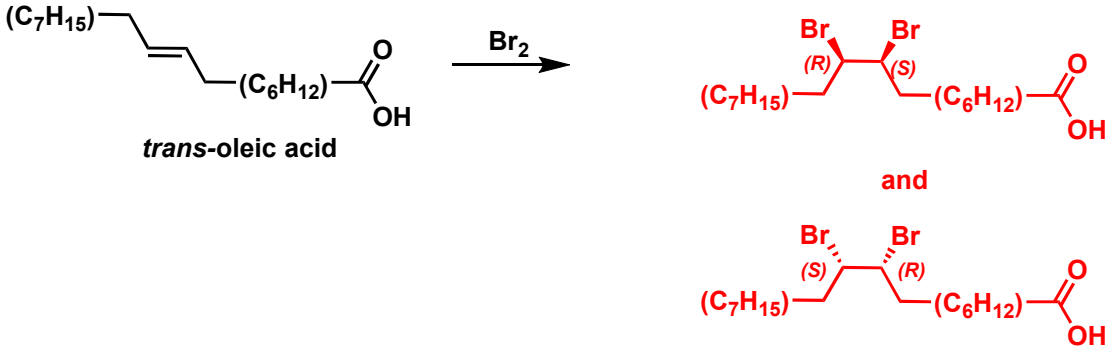
***cis*-oleic acid**



(+ enantiomer)



4-b. Based on the mechanism you provided in part **a**, predict the product(s) of the bromine test with *trans*-oleic acid, clearly indicating the appropriate relative and absolute stereochemistry.



***trans*-oleic acid**

4-c. The products in parts **a** and **b** are: *(circle one and justify your answer)*

structural isomers ***diastereomers*** ***enantiomers*** ***identical molecules***

Because dibromination proceeds with a stereospecific mechanism, the two bromine atoms will always be installed anti to each other. As such, changing the configuration of the double bond will cause one of the two stereocenters to differ in the product.